Armed Forces College of Medicine

AFCM

Molecular basis of muscle contraction and its metabolism

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INTENDED LEARNING OBJECTIVES (ILO)

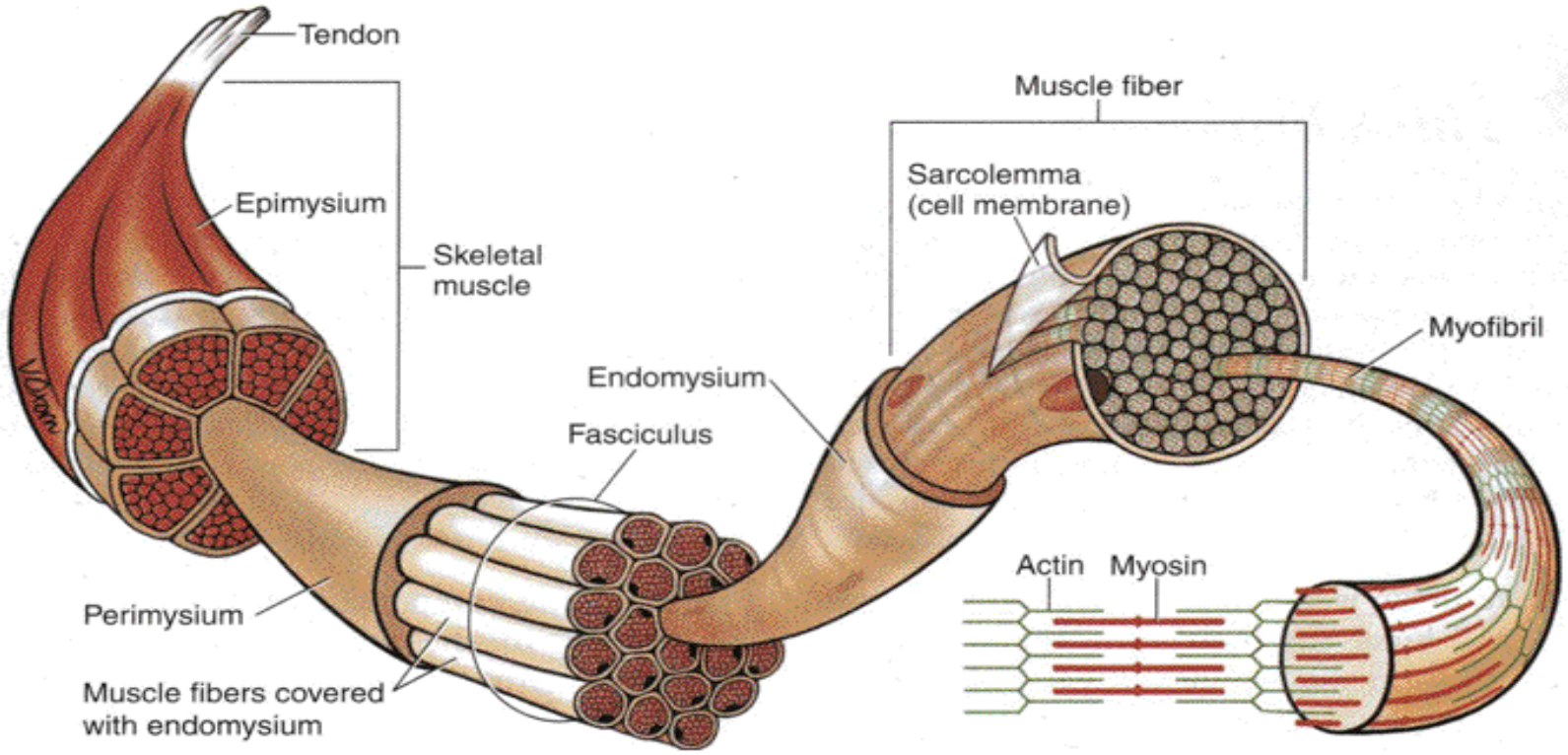
By the end of this lecture the student will be able to:

1. Describe skeletal muscle structure–function relationships.
2. Summarize the excitation-contraction coupling.
3. Recognize the mechanism of cross bridge cycle
4. Interpret the role of cytosolic calcium in muscle contraction and relaxation.
5. Identify different energy sources supplied to the muscle
6. Describe the importance of each energy source system
7. Define the oxygen debt
8. Identify the types and the importance of oxygen debt
9. Identify causes of muscle fatigue

Lecture Plan

1. Structure function relationship(15 min)
2. Cross bridge cycle and role of calcium (20 min)
3. Skeletal muscle metabolism (10 min)
4. Summary (5 min)
5. Lecture Quiz (5 min)

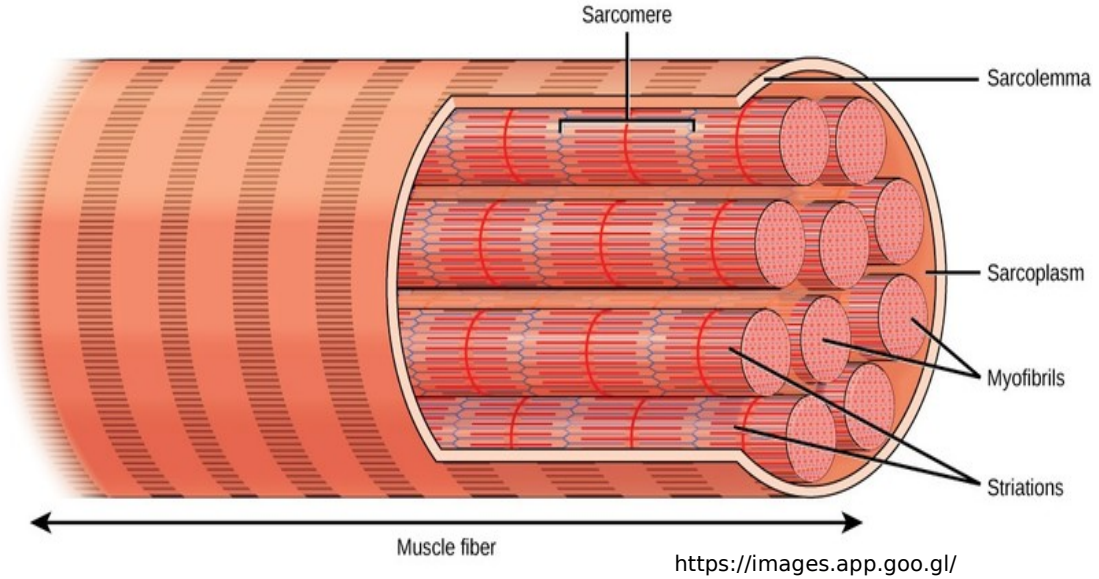
Skeletal muscle structure-function relationship



Kraemer, W.J., et al. (2011). Exercise Physiology: Integrating Theory and Application. Lippincott, Williams and Wilkins.

Skeletal muscle structure-function relationship

- Muscle fiber sarcoplasm contain two myofilaments types:
  - ❑ Thick myosin
  - ❑ Thin actin
- Myofilaments are arranged to form the **sarcomere.**
- Sarcomere is the **functional contractile unit** of the muscle fiber



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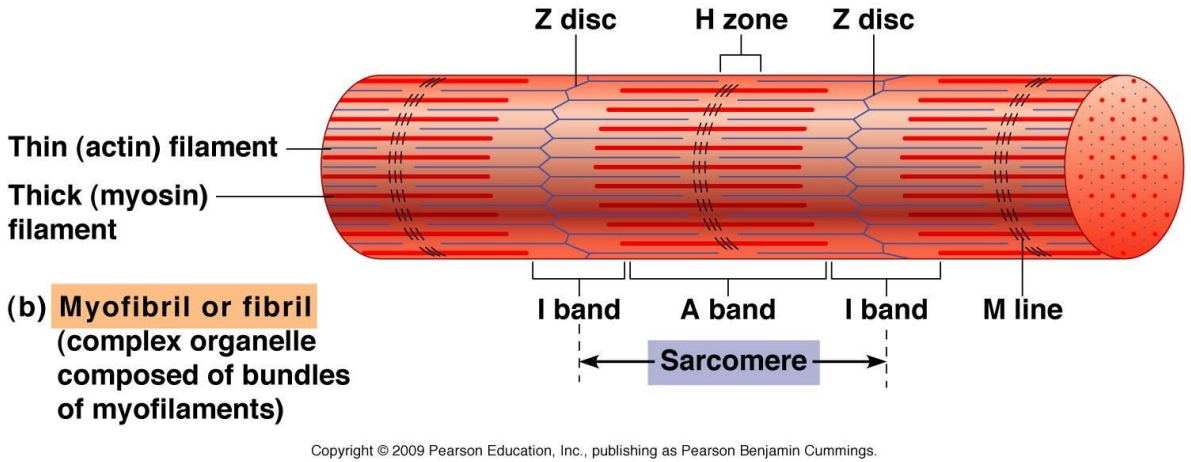


Muscle contract by sliding filament theory:

Sarcomere changes during muscle contraction

- The contraction of the muscle cell occurs as the thin filaments slide past the thick filaments.

Thick and thin filaments size do not change

Dark A band:

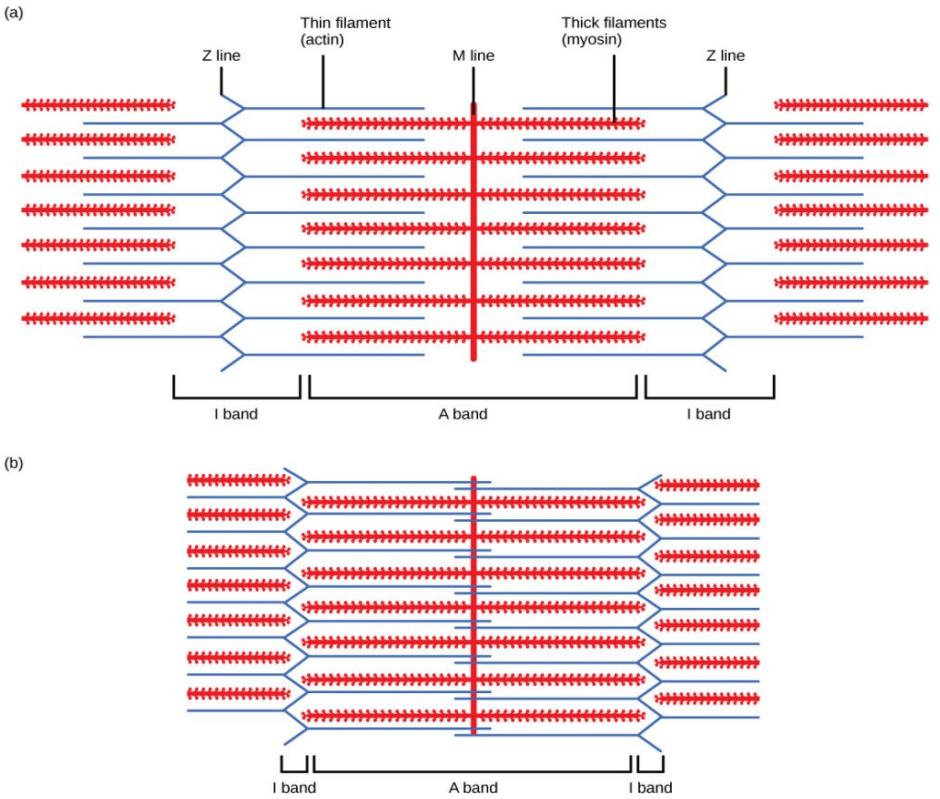
- Formed of thick myosin myofilament
- **Not shortened during contraction**

Light I band:

- Formed of thin actin myofilaments not covered by myosin
- **Smaller during contraction**

Z lines:

- Connect thin filaments
- Sarcomere is the distance between 2 Z lines
- **Z lines Come closer during contraction, sarcomere shortens**



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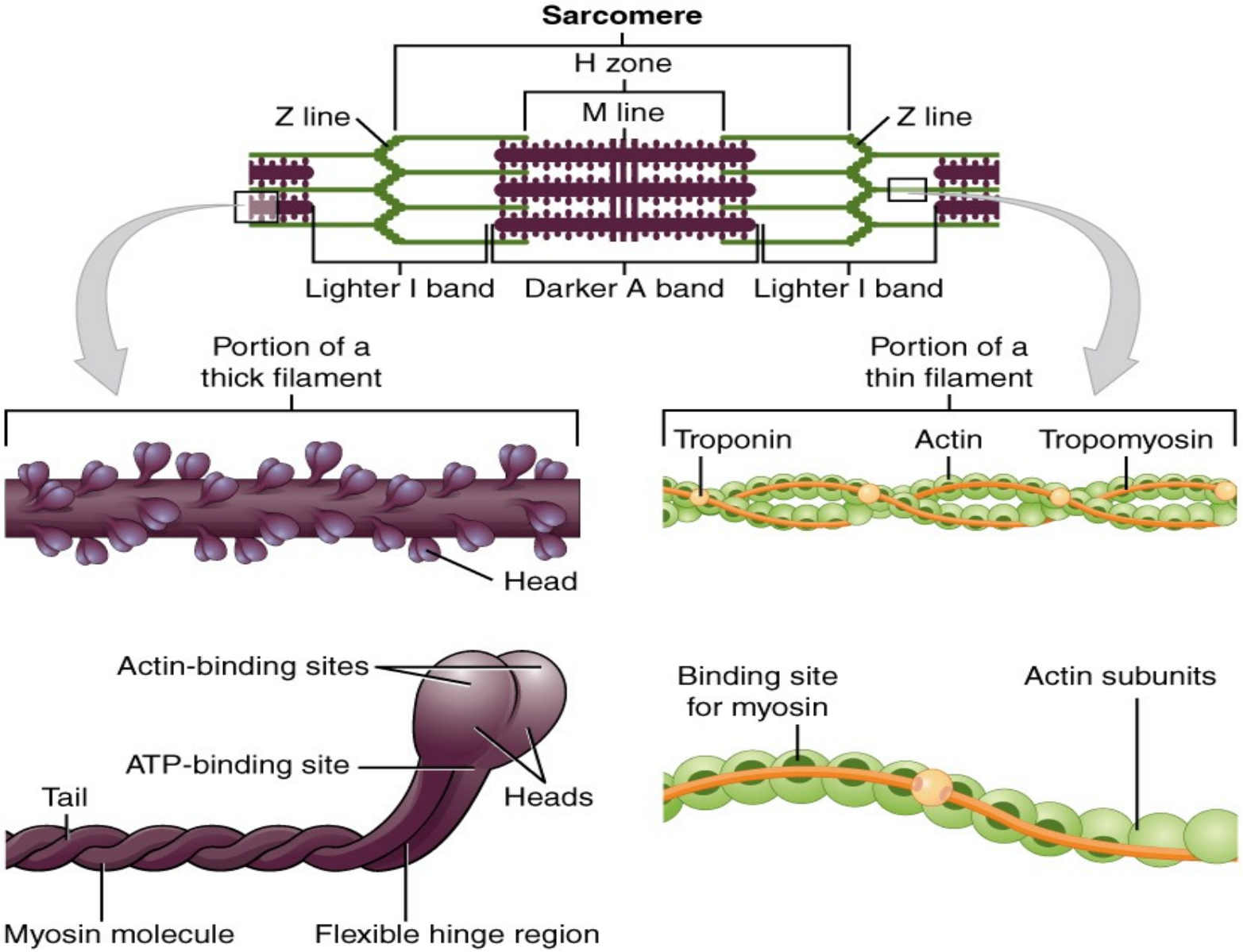
The muscle Myofilaments



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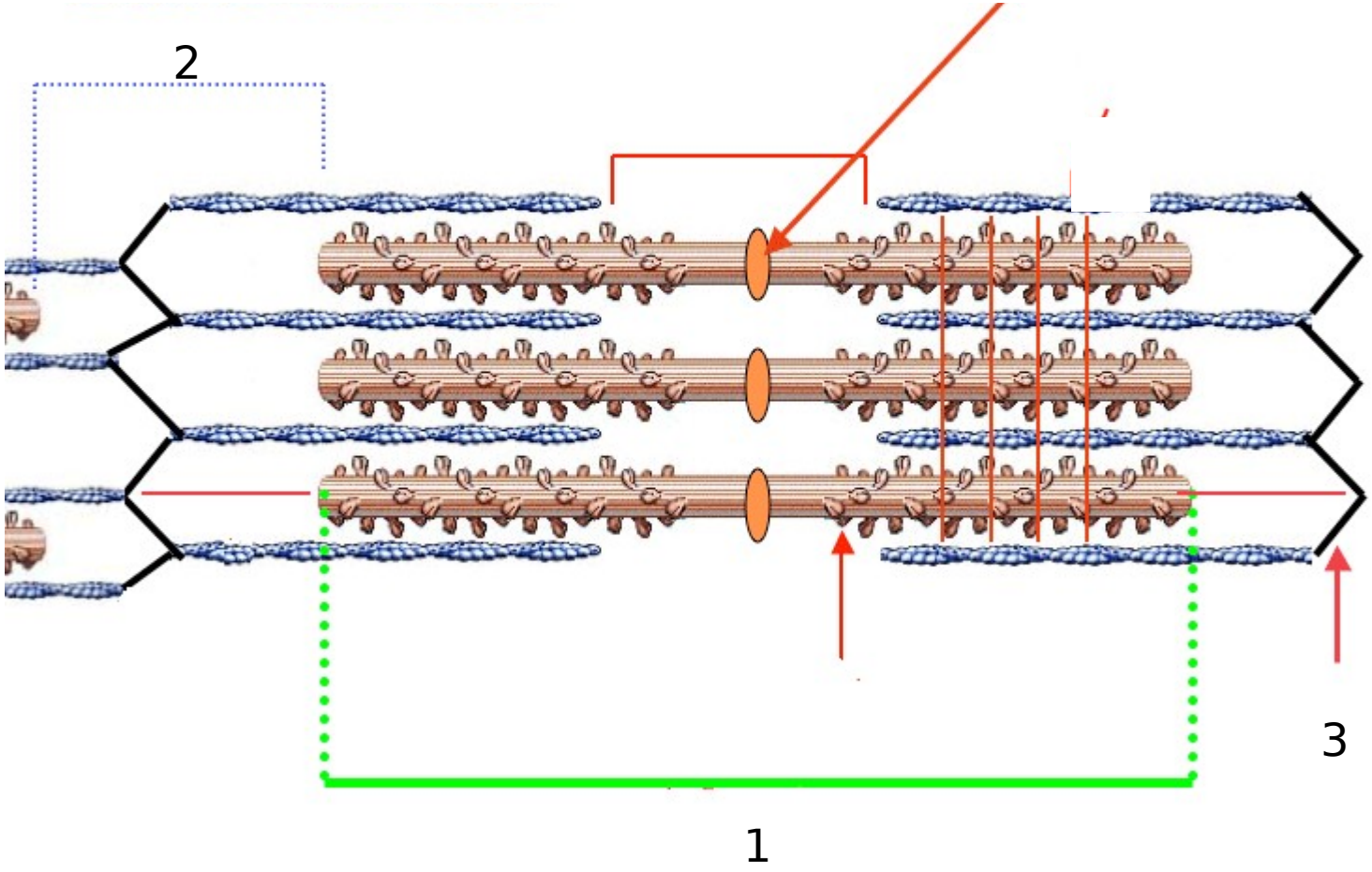


- **Q1-Which of the following is Thick myosin band?**

1------2----------3

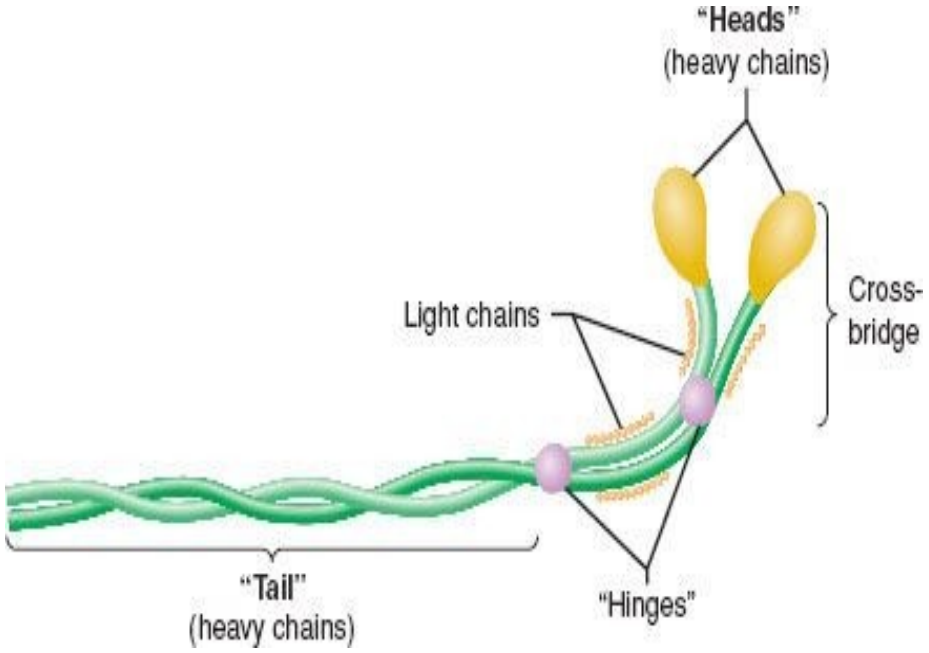
Q2- Do myosin band shorten during contraction?

Q3- Which of the following labels becomes shorter during contraction?

Thick myosin

- **Tail:** 2 heavy polypeptide chains coiled forming a double helix
- **Arm:** extended part of the tail, form with the head **cross bridges** that can move back and forth
- **2 Hinge portions of the tail:**

➢ First: allow **vertical movement**, so that the cross bridge can **bind to**



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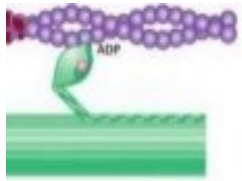
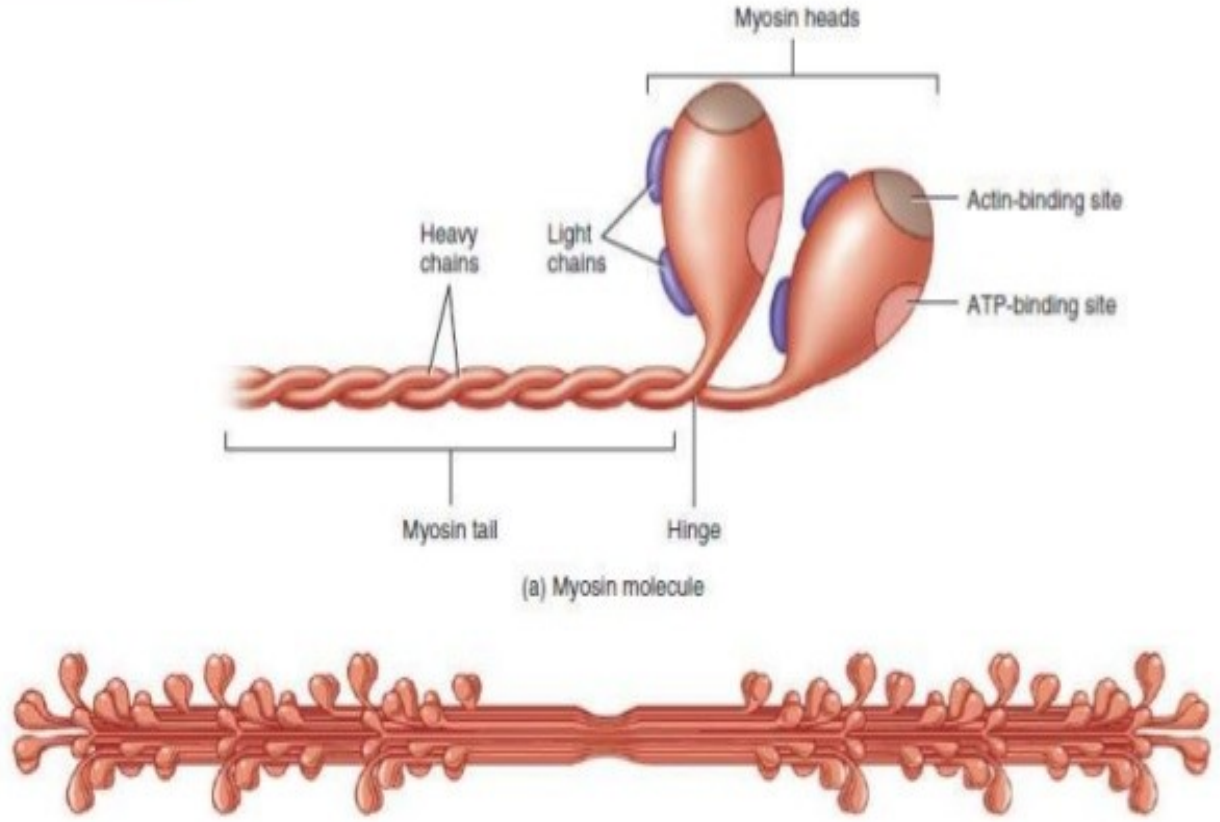
Thick myosin

- **Myosin head contains 2 binding sites:**

➢ **ATP binding site:** This site has ATPase activity. When ATP molecule binds, it is hydrolyzed into ADP, Pi + energy. The energy is transferred to myosin head (i.e. energizing myosin head).

- **Actin binding site:** This site has a strong attraction for binding to actin.





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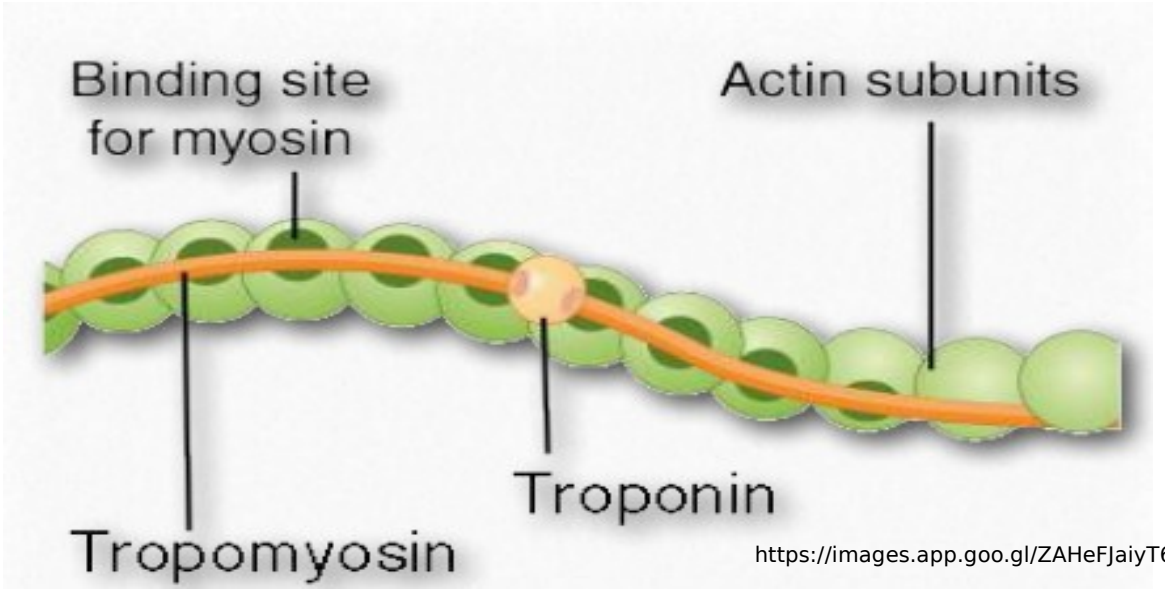
Thin actin

1-Actin double helix:

Double helix with specific myosin binding site (active site) for the attachment of the myosin cross bridges.



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2-Tropomyosin:

Relaxing protein that blocks the interaction between actin and myosin cross bridges by covering the myosin binding sites

3- Troponin protein complex:

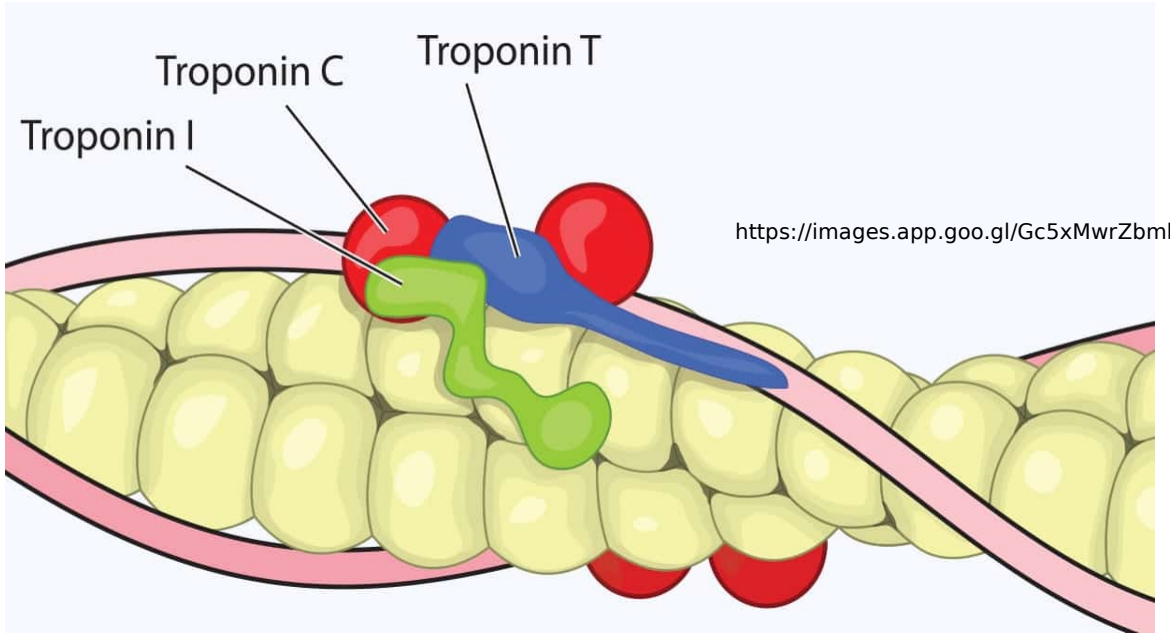
- **Troponin T:**

Fix tropomyosin to cover active sites during muscle relaxation

- **Troponin C:**

Bind calcium to initiate contraction

- **Troponin I:**



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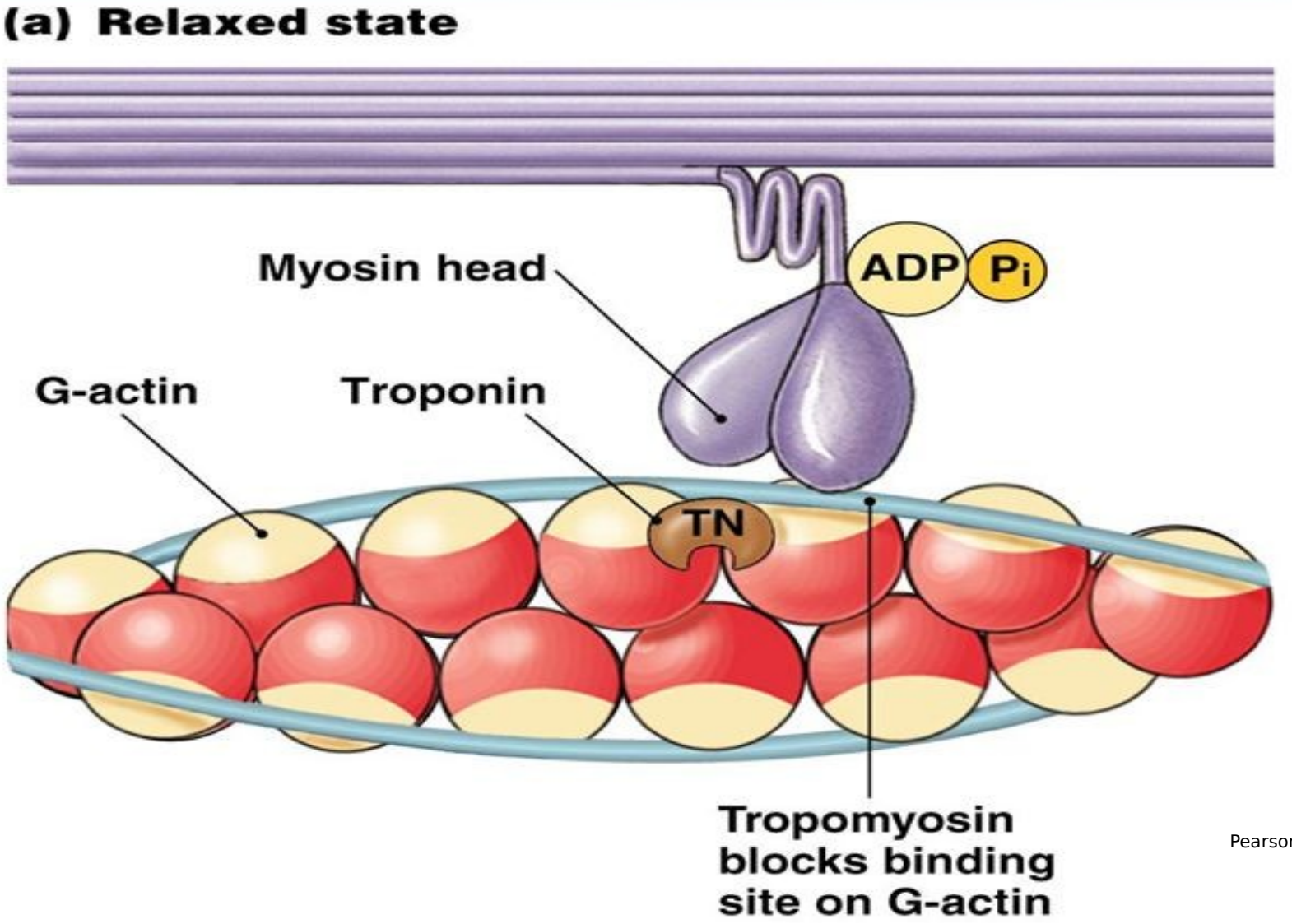
Regulatory Role of Tropomyosin and Troponin

In the relaxed state the myosin head is at 90o but it is unbound to actin because the binding sites on actin are blocked.

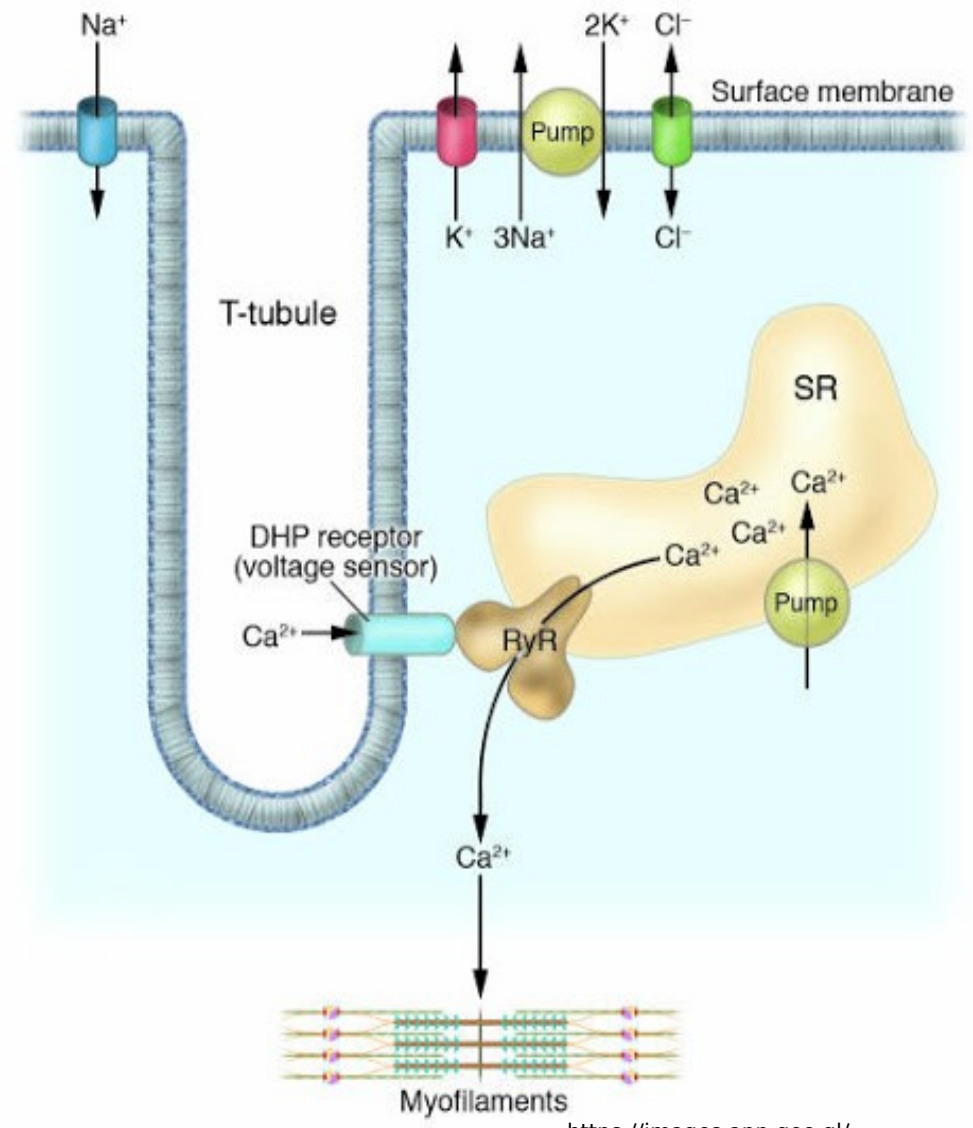


Pearson education

Excitation contraction coupling

- It is the process by which depolarization of the muscle fiber initiates muscle contraction.

1. Depolarization wave spread inward along T tubules
2. Conformational changes in **dihydropyridine receptors (DHP) the voltage sensor**
3. Mechanical coupling (connection) between DHP



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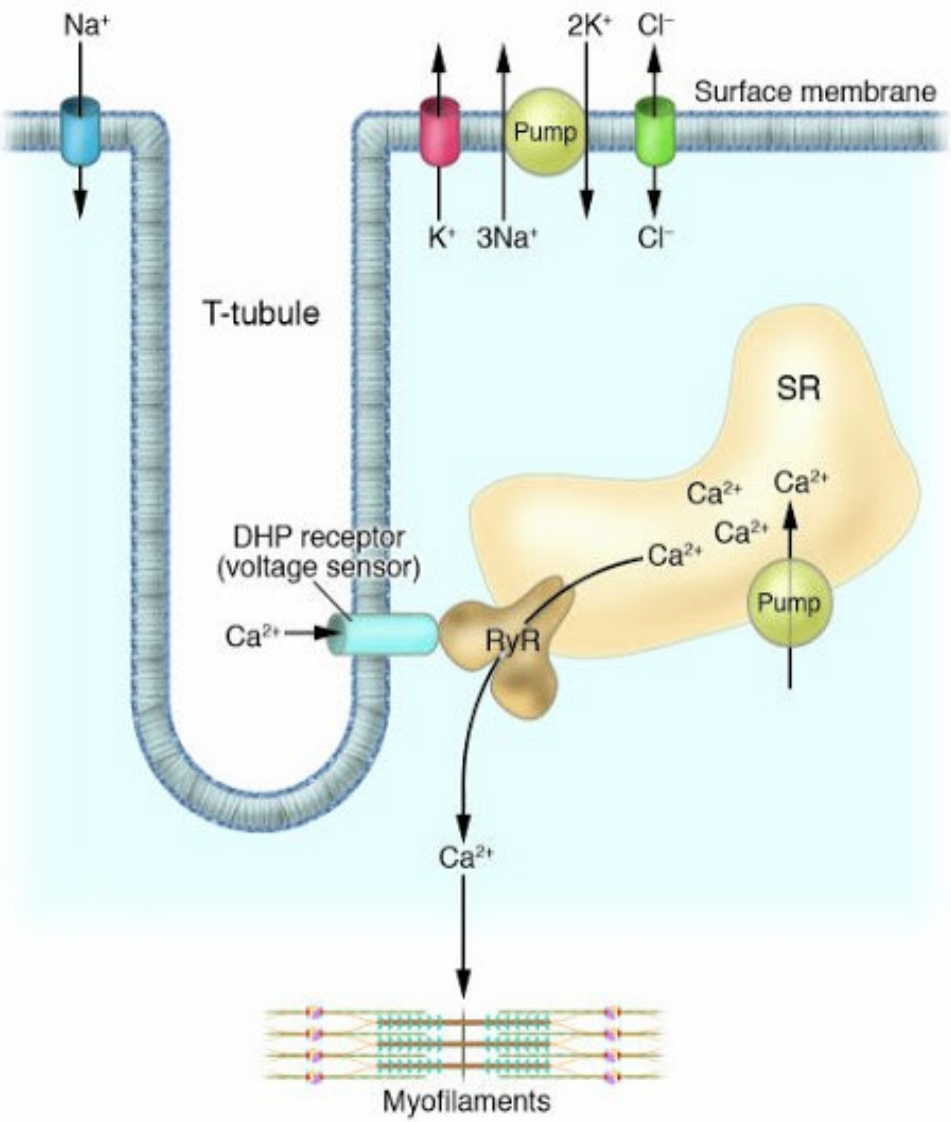
Excitation contraction coupling

4. The sarcoplasmic reticulum (SR) has a **high concentration of Ca2+**. Thus, there is a strong electrochemical gradient for Ca2+ to diffuse from the SR into the cytosol.
5. This allows Ca++ exit from the terminal cisterns of the SR into the cytoplasm of the muscle fiber.
6. Increase sarcoplasmic calcium

Calcium



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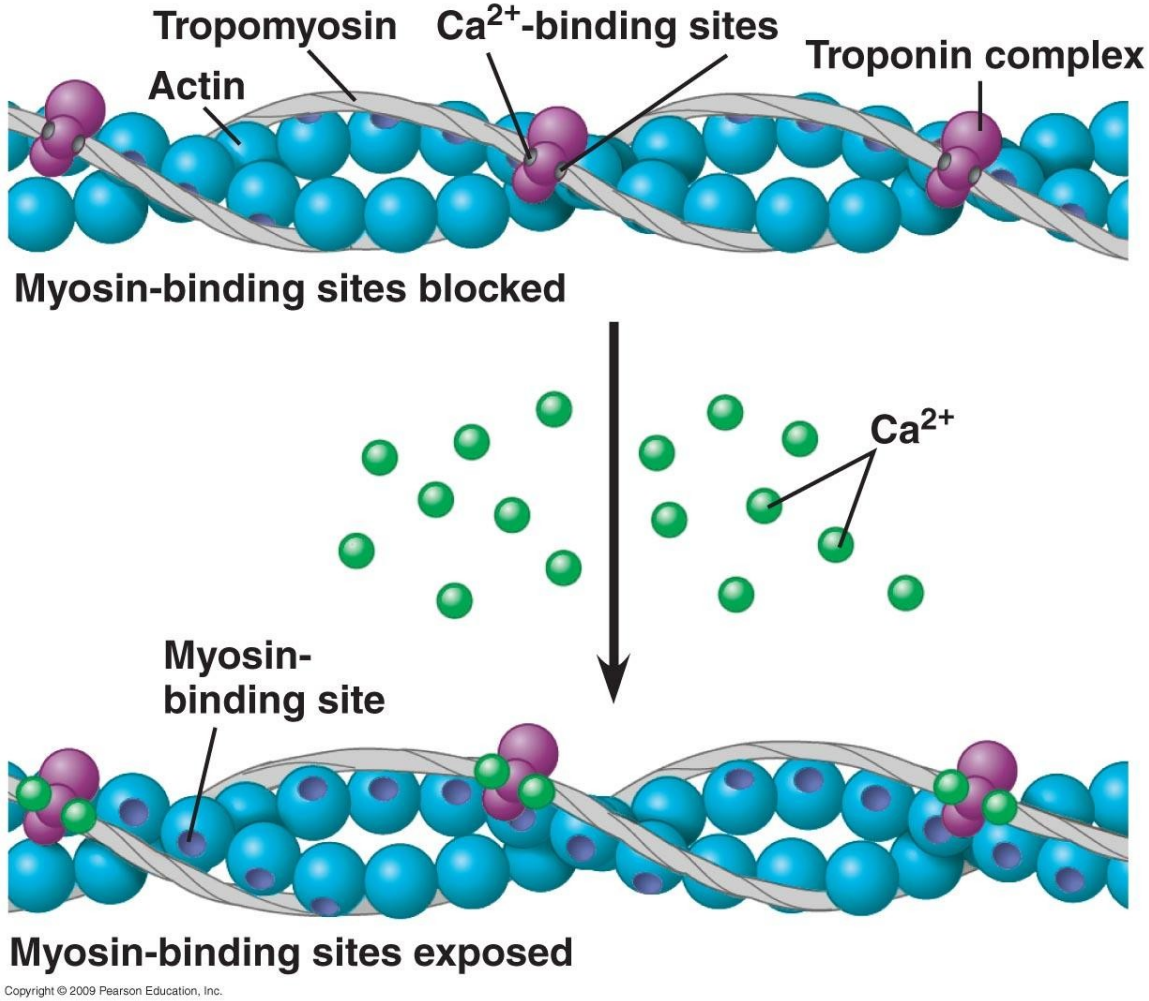
Excitation contraction coupling

6-Binding of **calcium to troponin C**, induce conformational **change in troponin-tropomyosin complex**.

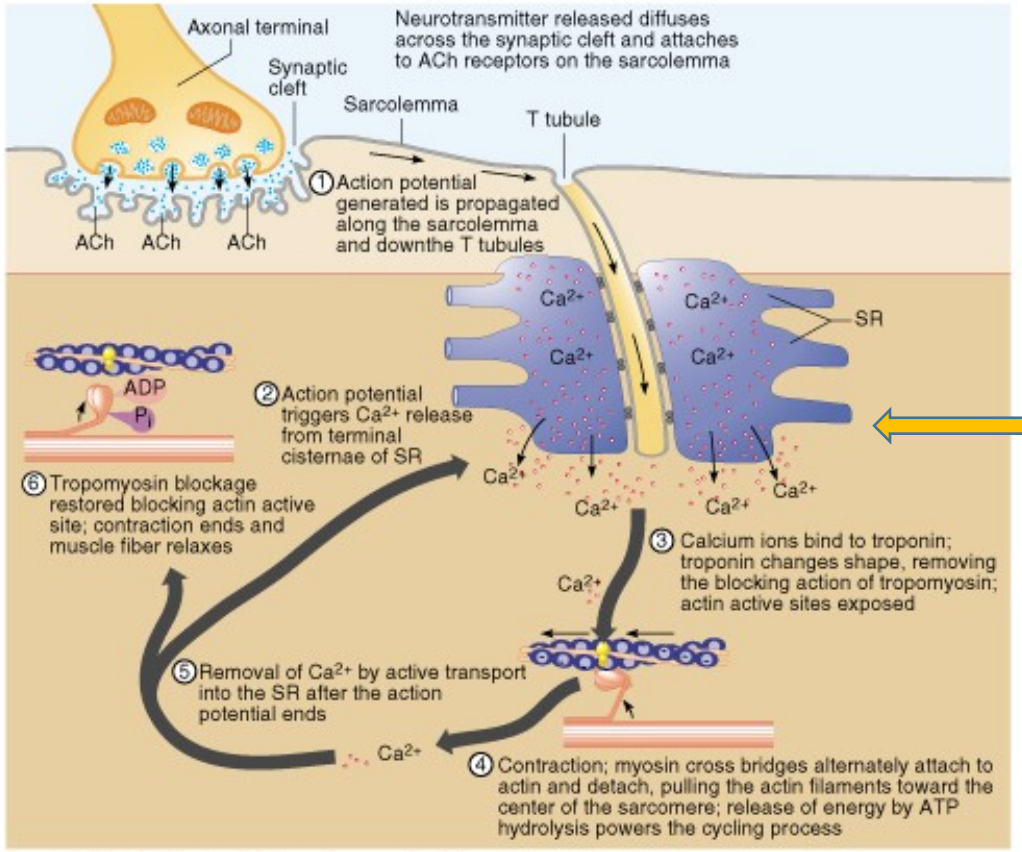
7- Tropomyosin moves laterally **exposing "uncovering" the myosin binding sites** on the actin

8- Cross linkages between myosin and actin, the start of cross bridge cycle



- ---------- is high in sarcoplasm during contraction.
- What is the source of calcium in skeletal muscle?

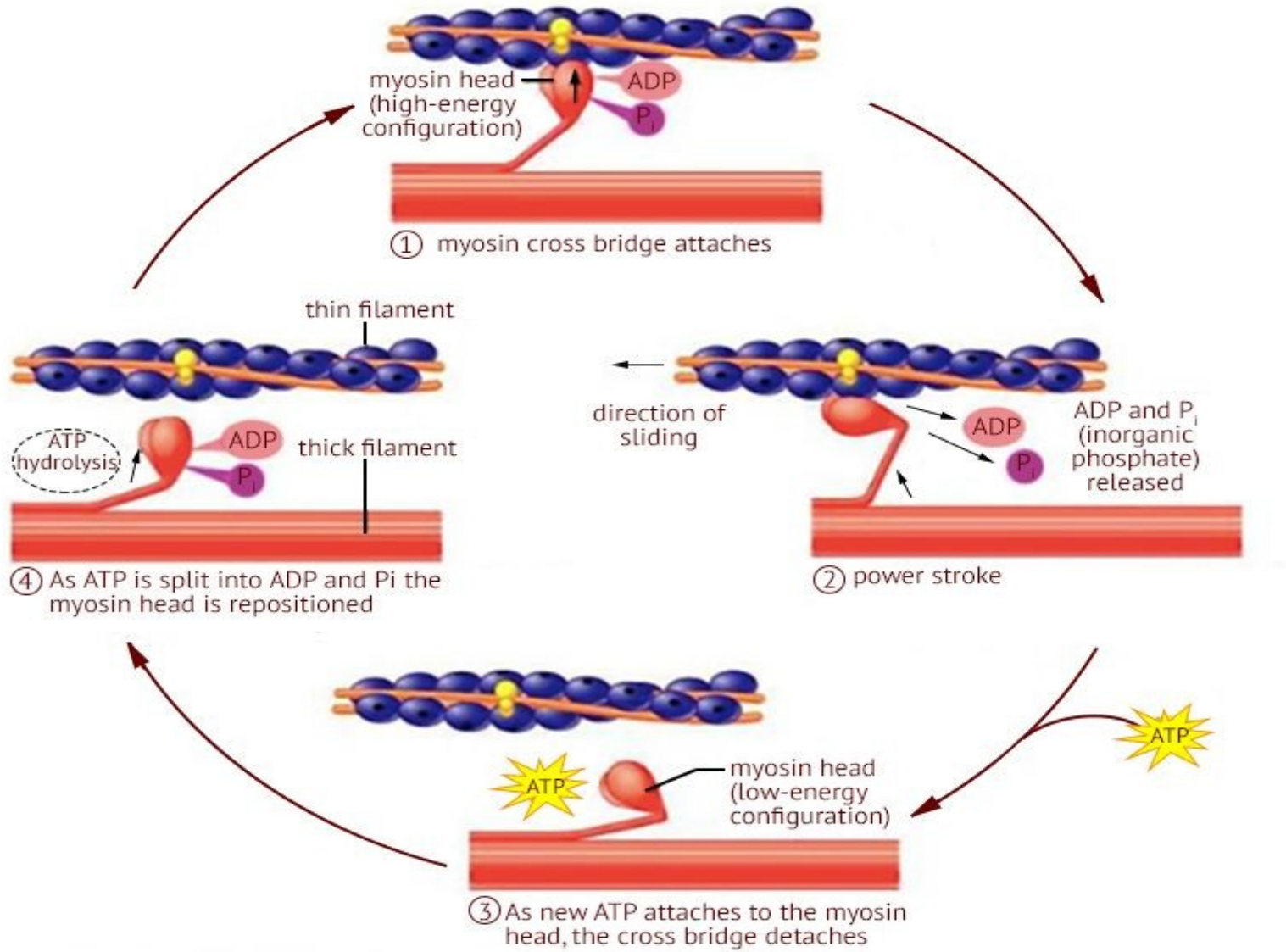
calcium



Sarcoplasmic reticulum

Cross bridge cycle (Walk along theory)

1. Bind
2. Bend
3. Detach
4. Repositioning



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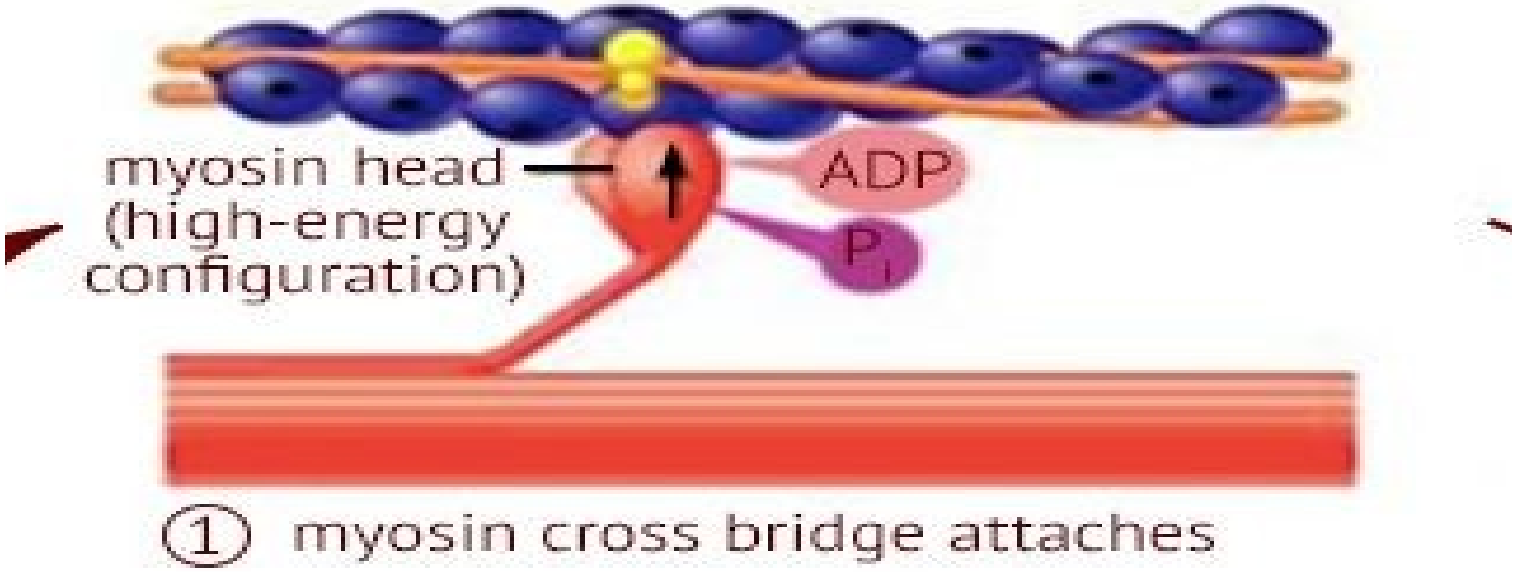
Cross bridge cycle



1. **<u>Binding:</u> Energized myosin** cross-bridge **has affinity for actin** and bind to the **exposed** binding site on actin

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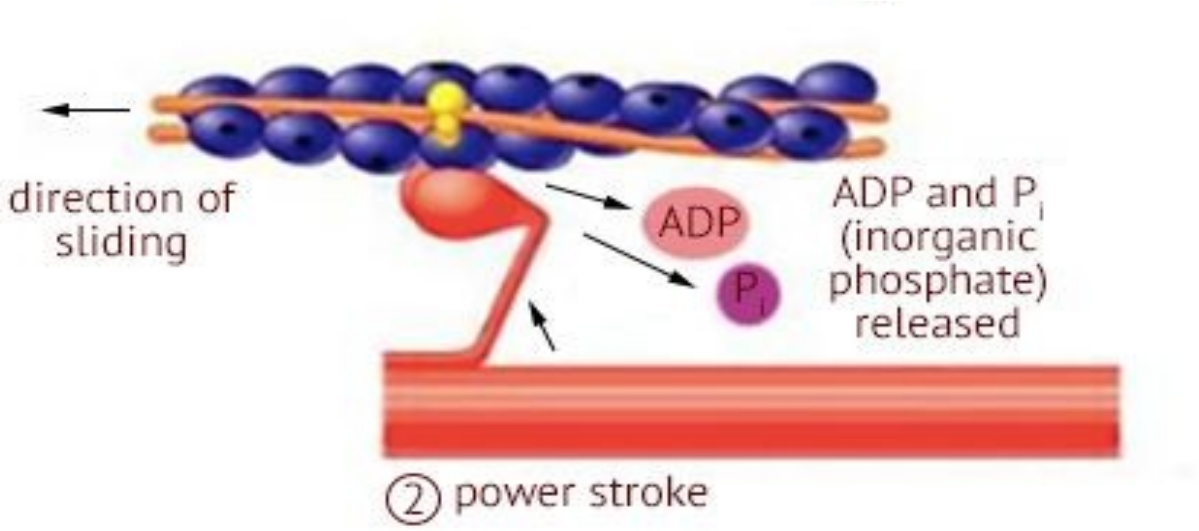
Cross bridge cycle



2-Bending (power stroke):

1. The cross bridge flexes (bends), pulling the thin filament inward towards the center of the sarcomere
2. At the same time, ADP and Pi. are released
3. Chemical energy is transformed to mechanical energy

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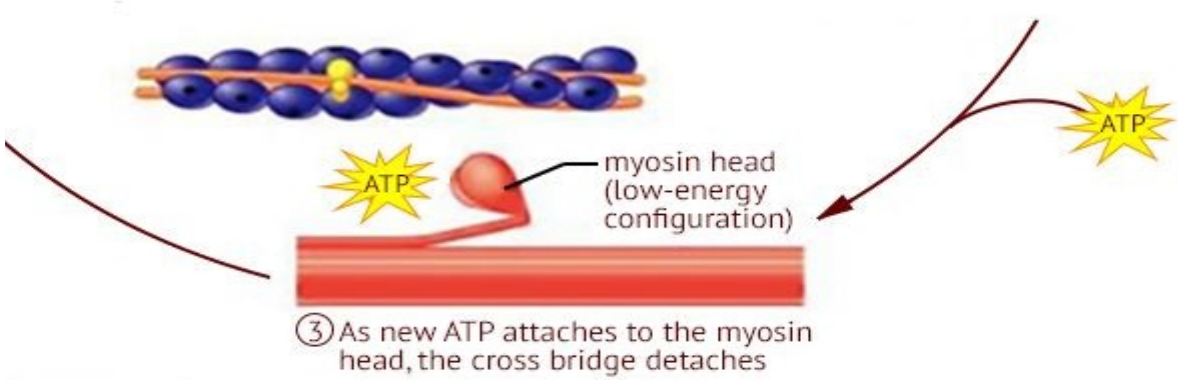
Cross bridge cycle



3-Detachment:

- A new ATP molecule bind to its site on myosin cross bridge
- Disconnection of the cross-bridge from actin

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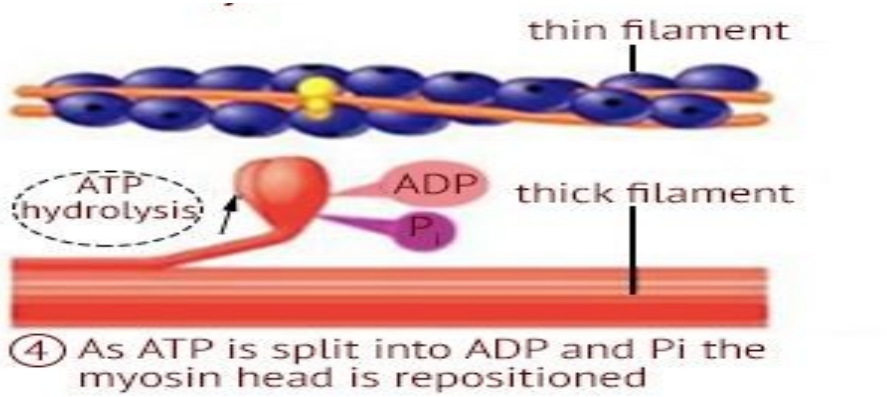
Cross bridge cycle



4-Repositioning:

- Re-energizing of myosin cross bridge: Hydrolysis of ATP molecule gives rise to ADP, Pi & energy.
- Energy is transferred to the which myosin cross bridge returns to its high-energy conformation
- Myosin returns to its normal perpendicular position (Cocked position) to bind to a new active site.

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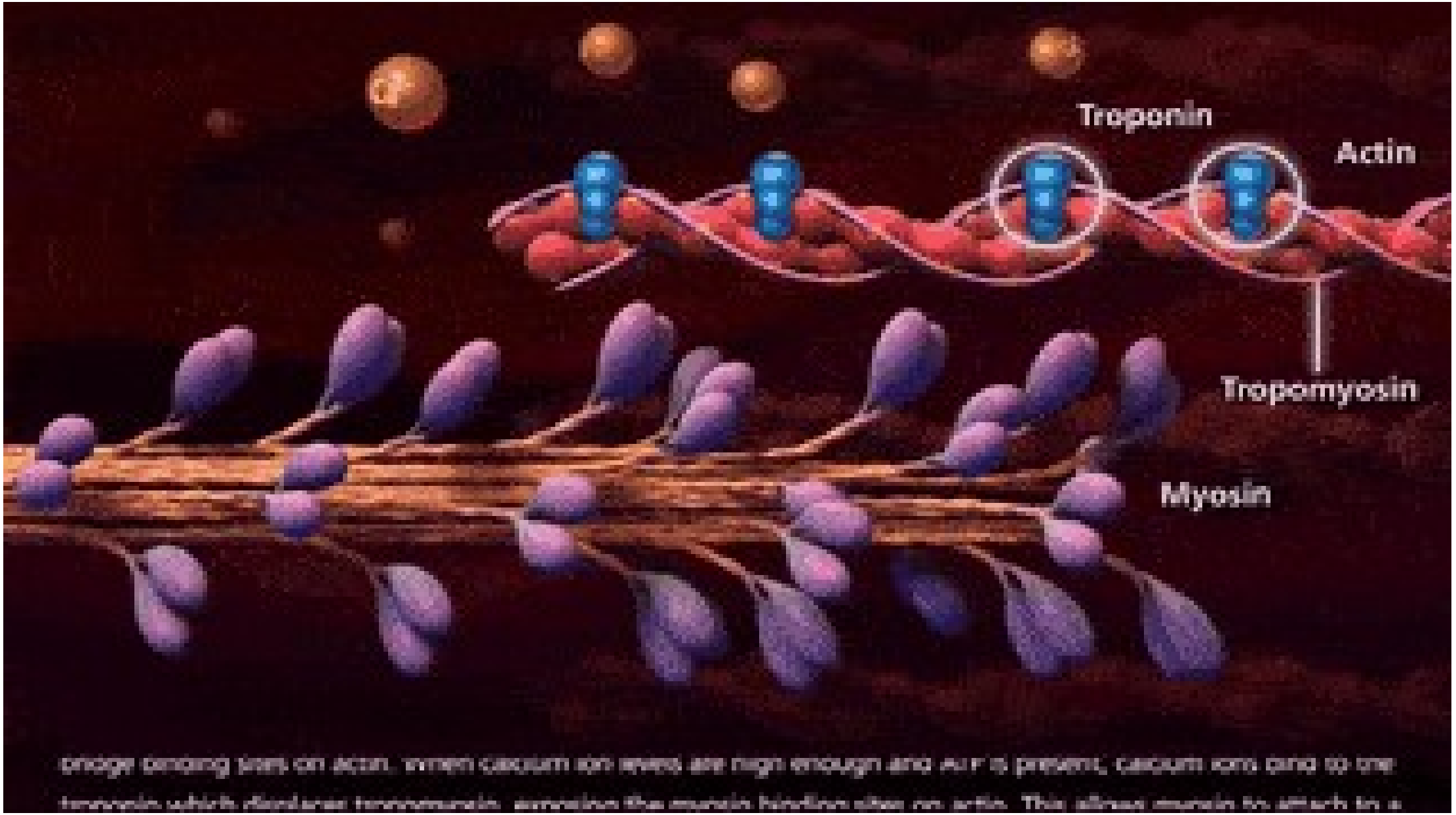
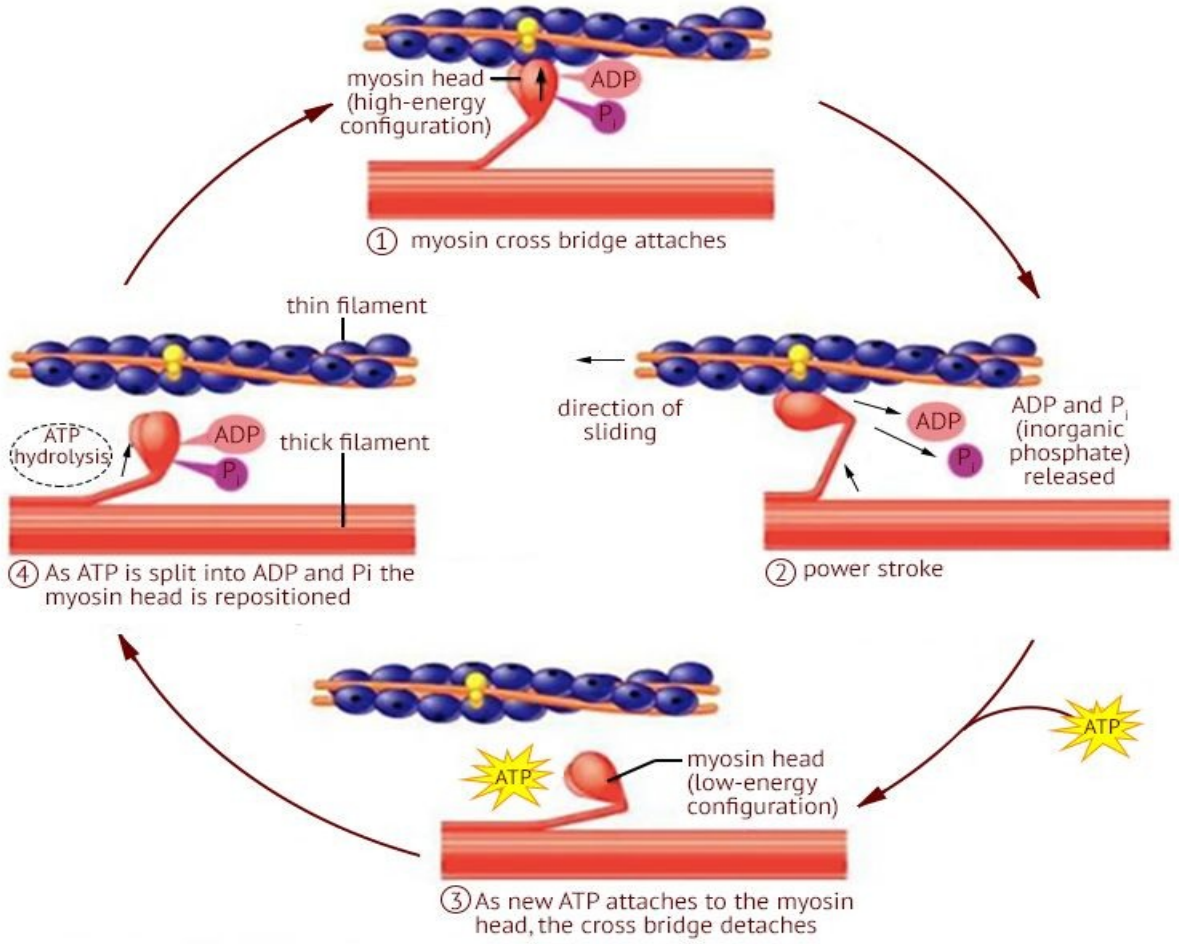

Troponin
Actin
Tropomyosin
Myosin

Cross bridge cycle (Walk along theory)

- During contraction, there are multiple cross bridge cycles
- The greater the numbers of cross bridges in contact with the actin filament, the greater is the force of contraction.
- Each one of the cross bridges is operating independently of all others
- But, the multiple cross bridge cycling is coordinated sequentially to prevent all cross bridges from either being connected or disconnected at the same time.



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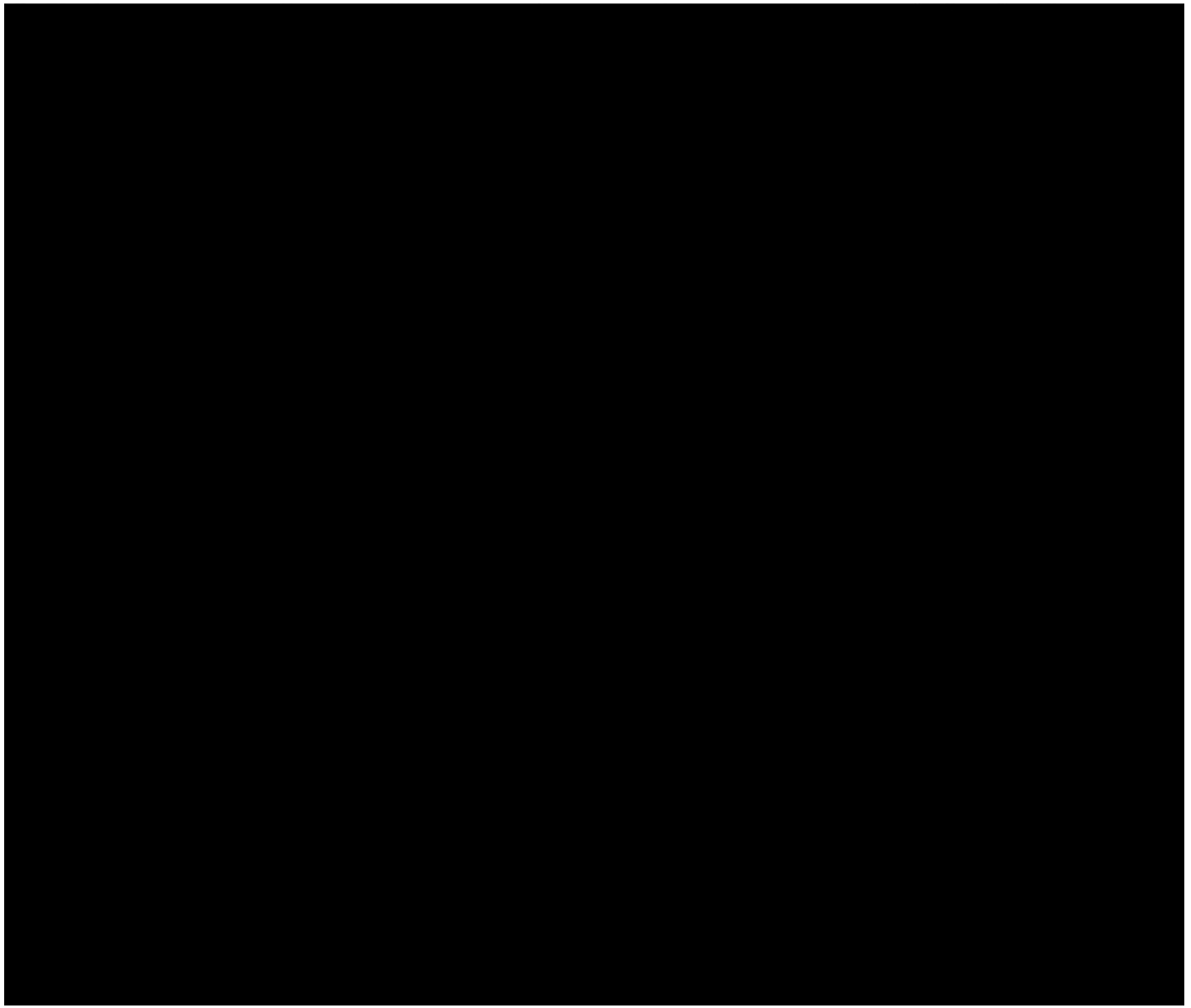
Role of Calcium in muscle contraction

- As long as Ca++ ions are available
- The cross bridge cycles are repeated
- Muscle contraction continues



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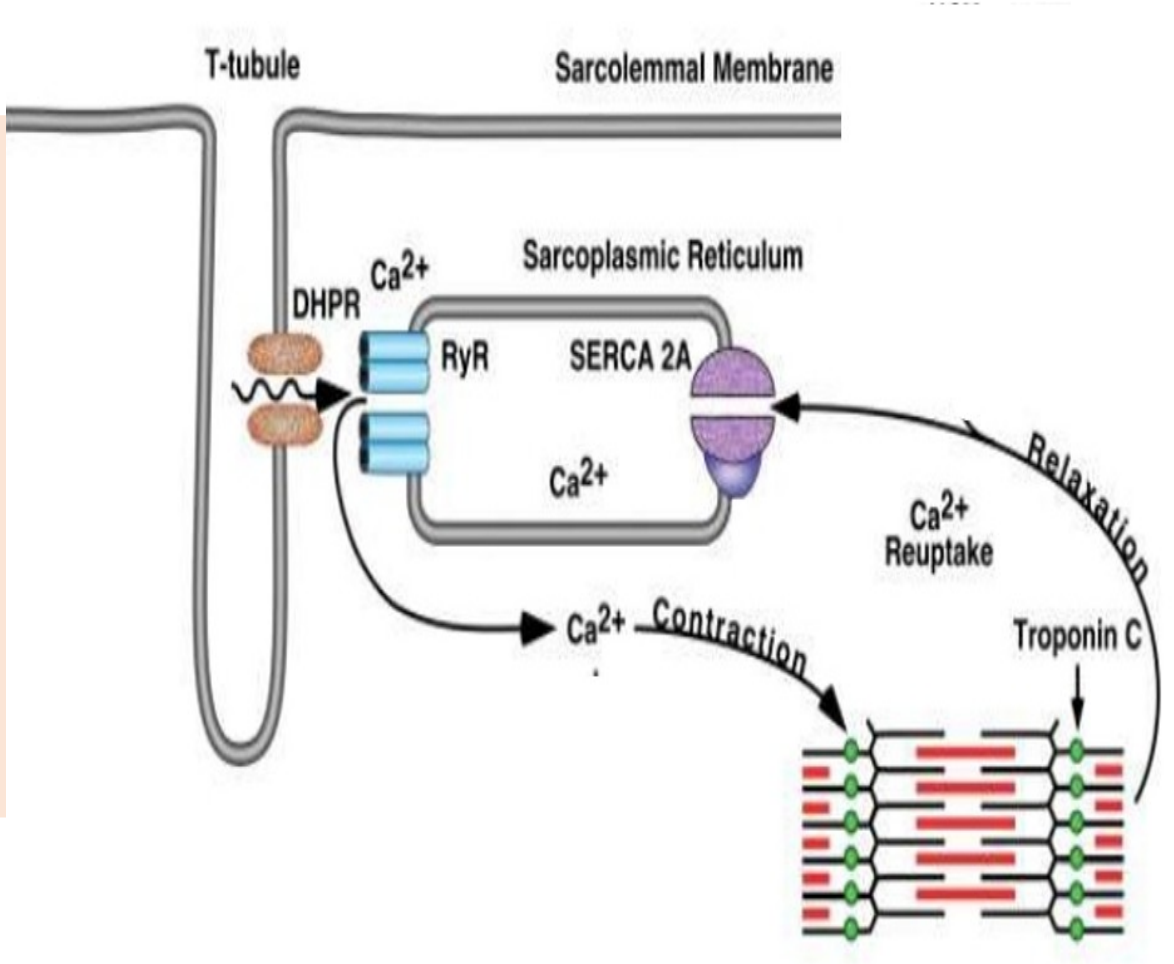
Muscle relaxation steps

- It is an active process.
- It depends on active reuptake of Ca++ into the SR by Ca++ pump.
- Return (reduction) of intra-sarcoplasmic Ca++ concentration to the resting level
- Release of Ca++ ions from troponin C.
- Tropomyosin moves back to cover the active sites on actin.
- Cessation of the interaction between actin and myosin.



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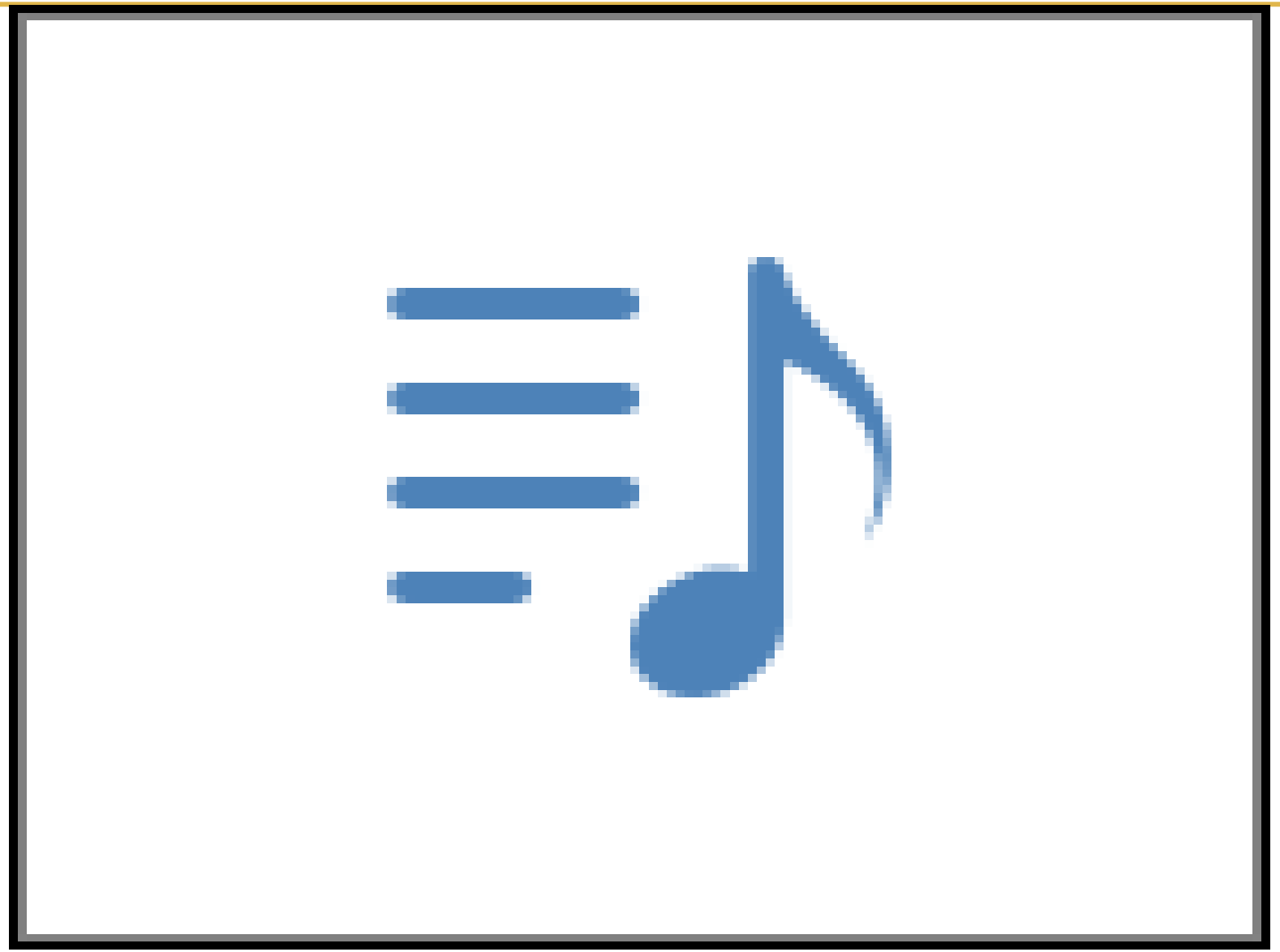
- **Rigor mortis**
- **Muscle contracture**:

This is the photo of a dead body, could you explain this contraction?

Rigor mortis

- It occurs after death due to depletion of ATP.
- Ca++ pumps can not function
- Cross bridge cannot detach
- It remains within 24 – 48 hours until protein breaks down.

Cross bridge cycle Summary



Part I Quiz

1. What is the role of transverse tubules during excitation-contraction coupling of skeletal muscle?

- **a. Provide an inward path for spread of action potential.**
- **b. Serve as storage site for calcium ions.**
- **c. Connect the sarcomeres end to end.**
- **d. Allow Ca^{2+} influx through Ca channels .**

2. What is the source of calcium ions required during skeletal muscle contraction?

- **a. Extracellular fluid.**
- **b. Extracellular fluid and sarcoplasmic reticulum.**
- **c. Intracellular fluid and sarcoplasmic reticulum.**
- **d. Sarcoplasmic reticulum.**

Muscle energy sources

What are the regenerating pathways for ATP?

1) ***Ultra-rapid immediate system***

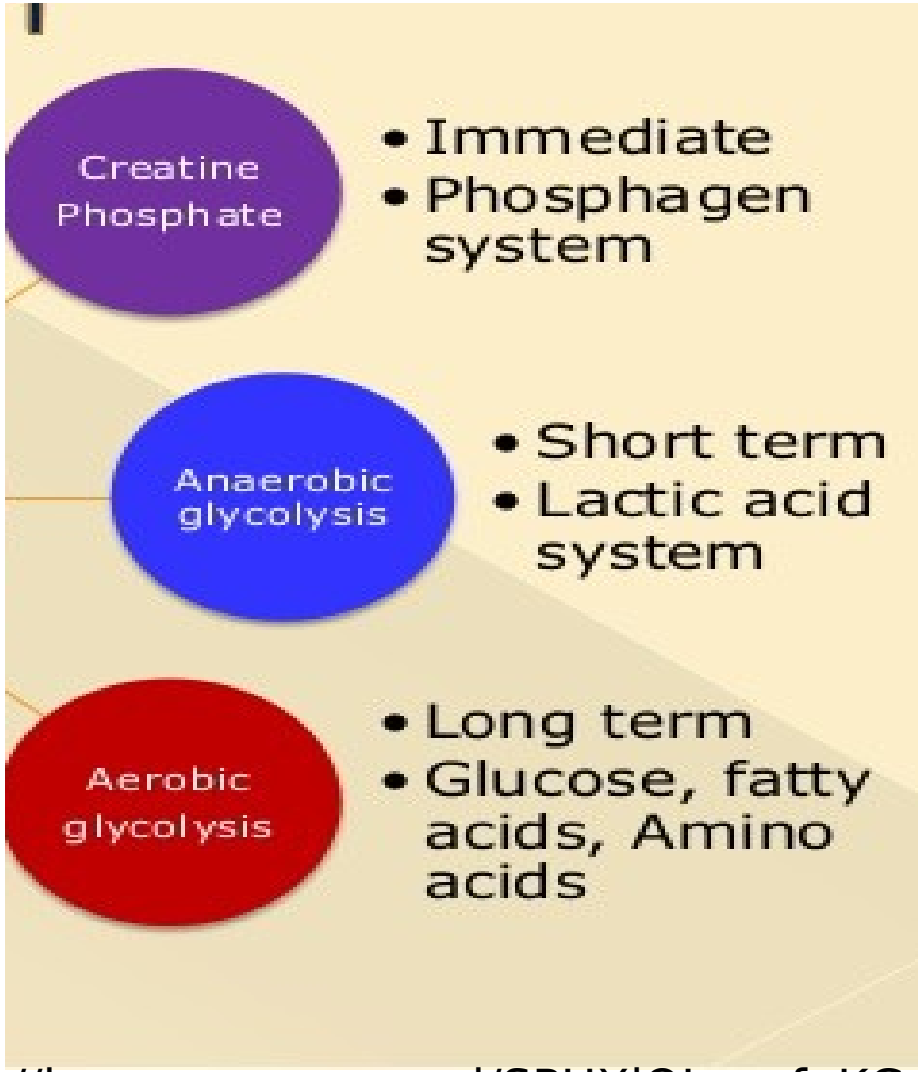
Hydrolysis of creatine phosphate.

2) ***Short-term anaerobic system***

Anaerobic glycolysis.

3) ***Long-term aerobic system***

Oxidative phosphorylation.



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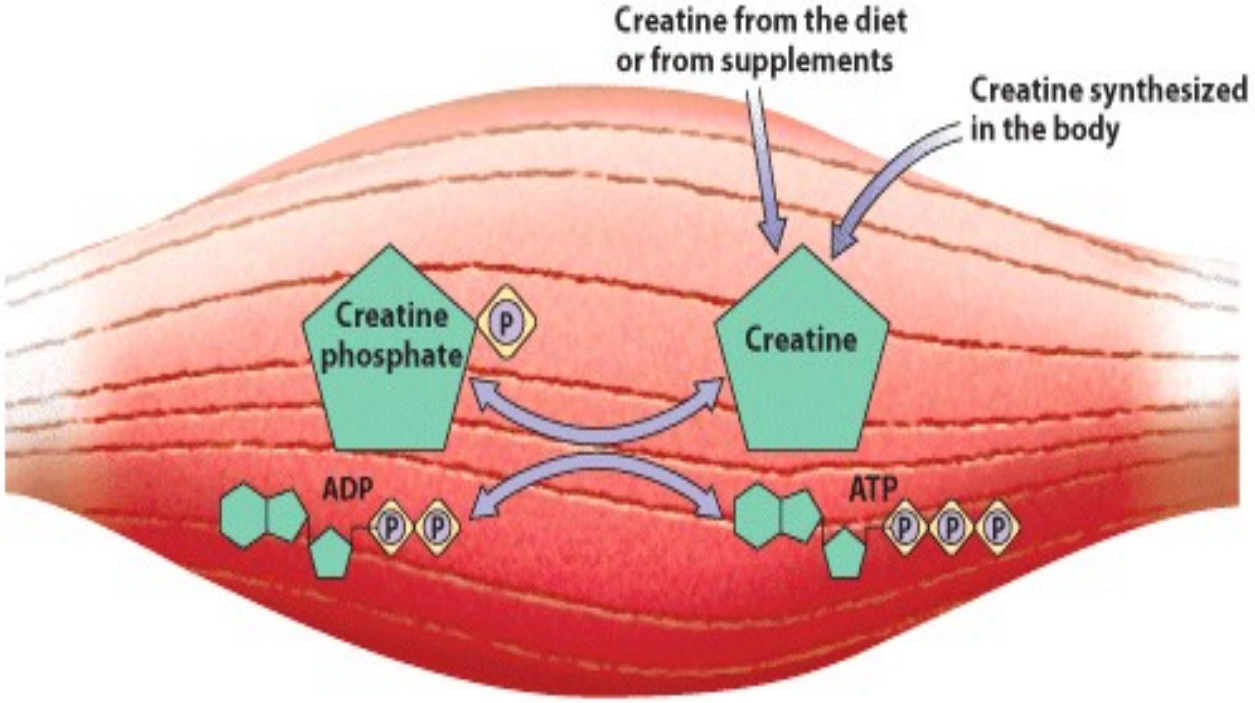
1: Ultra-rapid immediate sy

- **One molecule ATP** is formed per **one molecule** of **creatine phosphate** by substrate phosphorylation
- Immediate energy source in the **first few seconds**
- **High intensity short term exercise** as:
  - High jump
  - Weight lifting
  - 100 m running



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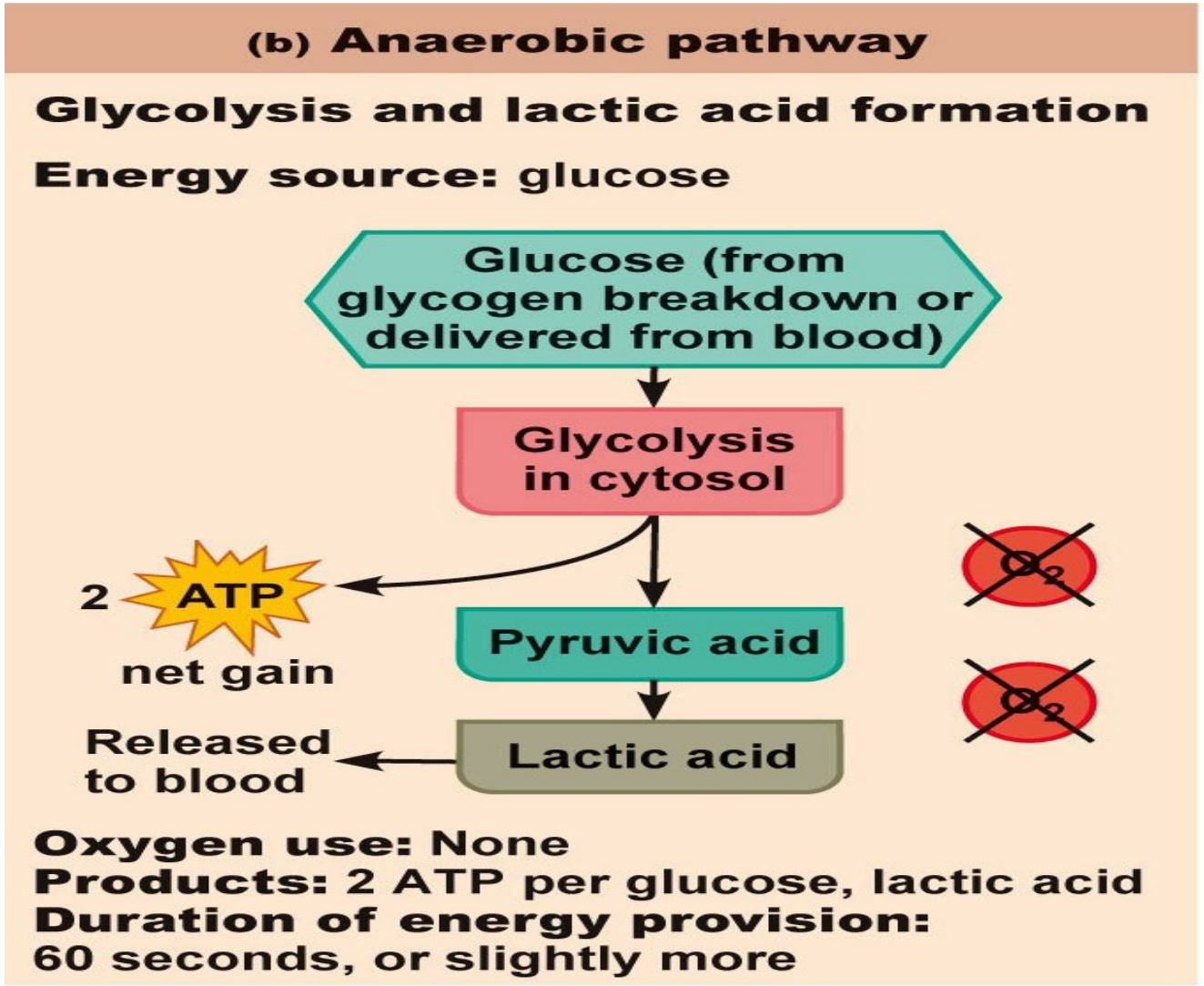
2: Importance of :
Short term anaerobic system

- **Fuel: glucose** is broken by **anaerobic glycolysis (oxygen absence)**
- **Source:** directly from blood or from glycogenolysis
- **End product:**

2 ATP molecules+ lactic acid

- **Importance:**
  - **Produce ATP 2.5 times as rapid as oxidative pathways**
  - **Few minutes at the start of exercise**
  - **At the end of the prolonged exercise when the aerobic system fails**
- Excess lactic acid causes fatigue



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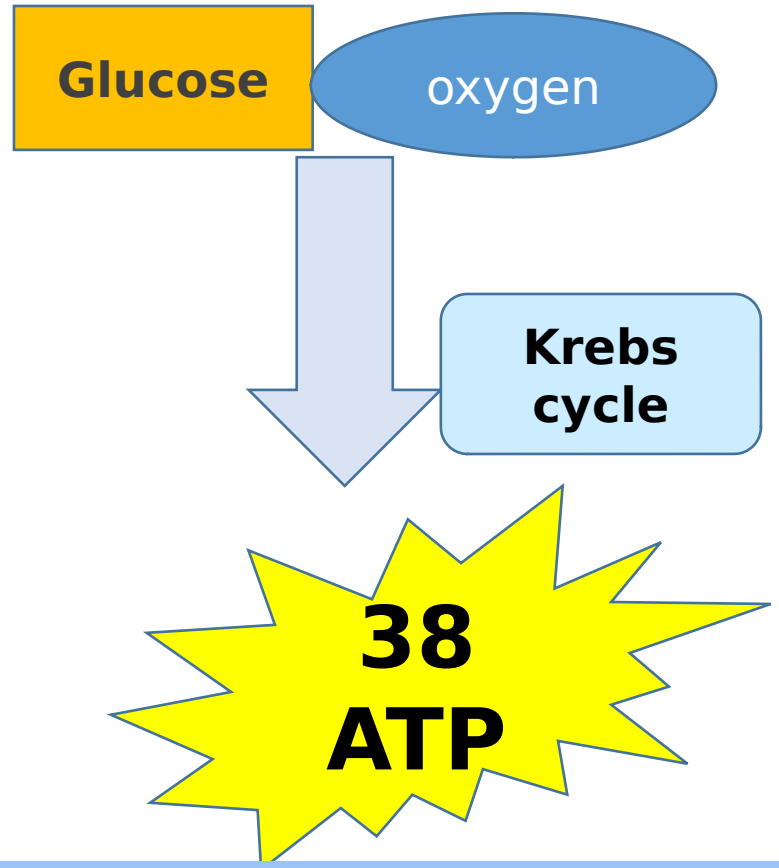
3: Importance of : Long term aerobic system

- **Fuel:** glucose mainly
- ***Oxygen source:***
  - Directly from blood
  - Stored in myoglobin (muscle oxygen containing molecule)
- **Aerobic endurance exercise or Light exercise**
  - Walking
  - Moderate exercise
  - marathon
  - Swimming



❑In prolonged light exercise more than 1 hour or in the resting muscle **free fatty acids oxidation** can supply energy

Explain the shift to anaerobic system at the end of exercise

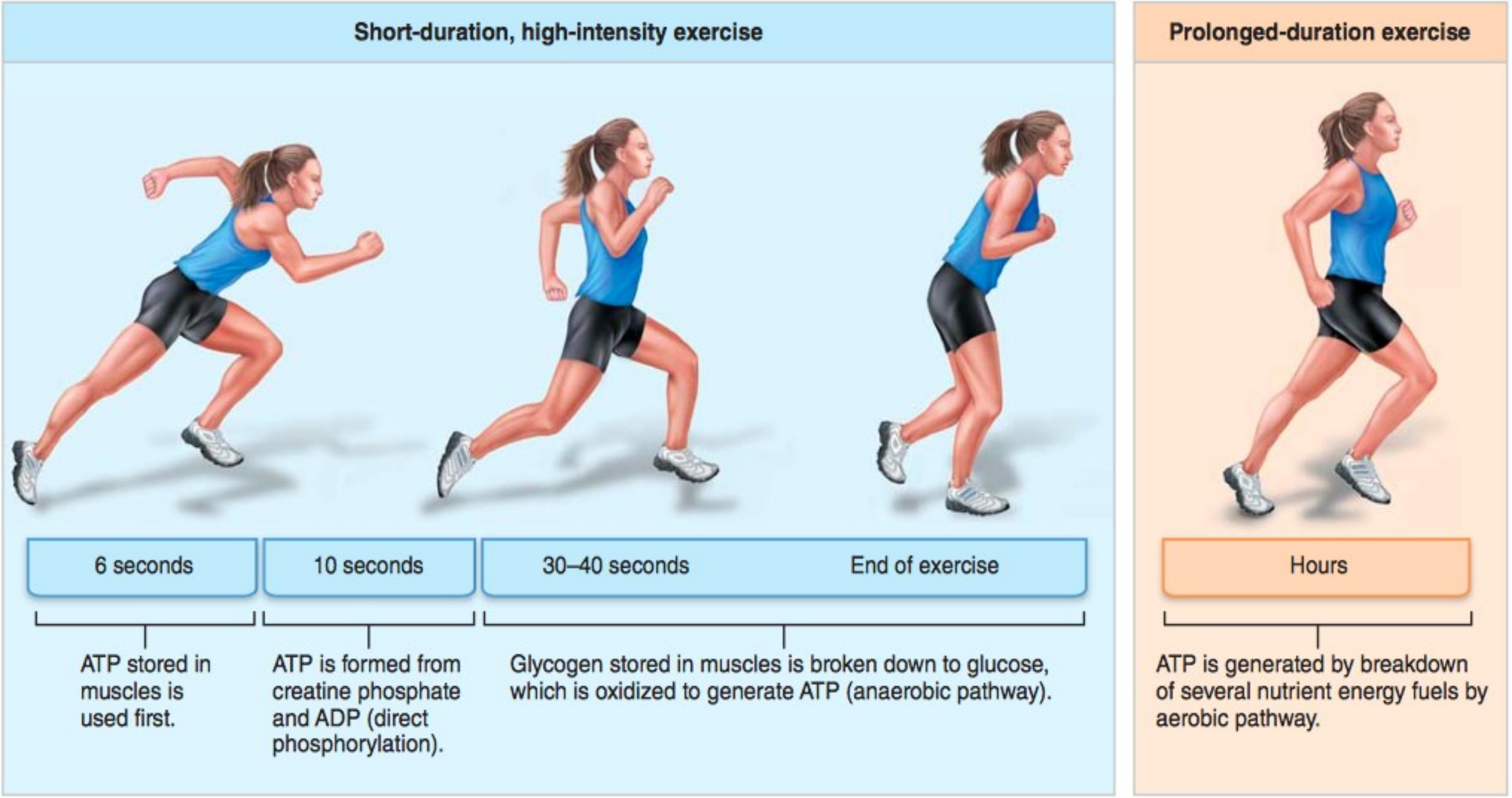
- Because the aerobic system is unable to meet the muscle demands.
- So anaerobic threshold is reached

❖ **Aerobic power** depend on:

➢ The lungs' ability to oxygenate the blood

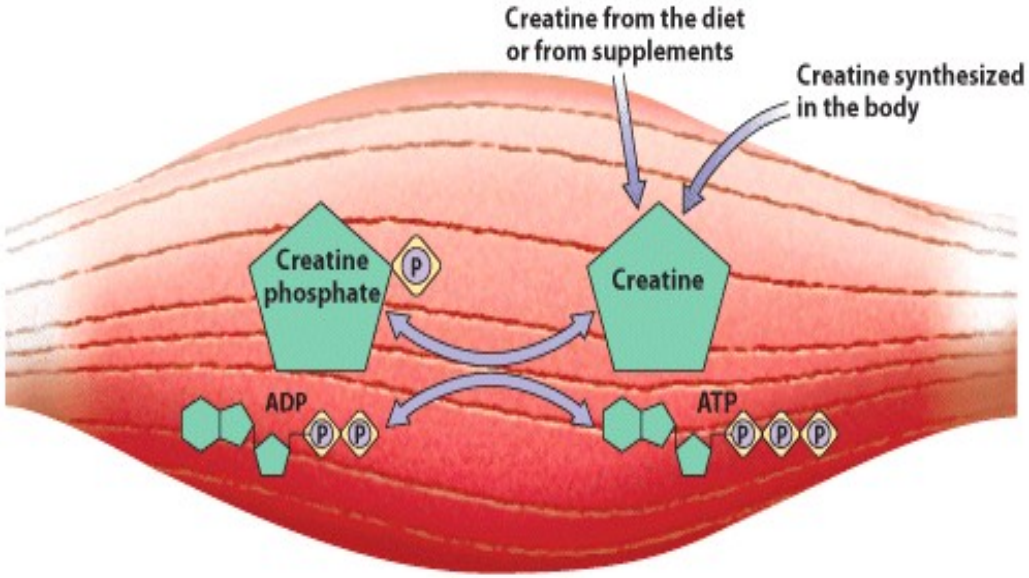
➢ The cardiovascular system's ability to deliver the oxygenated blood to the exercising muscles

➢ The muscles' ability to extract and utilize the oxygen to produce energy


Short-duration, high-intensity exercise
Prolonged-duration exercise
6 seconds
10 seconds
30–40 seconds
End of exercise
Hours
ATP stored in muscles is used first.
ATP is formed from creatine phosphate and ADP (direct phosphorylation).
Glycogen stored in muscles is broken down to glucose, which is oxidized to generate ATP (anaerobic pathway).
ATP is generated by breakdown of several nutrient energy fuels by aerobic pathway.

This athlete runs in a 100 m sprint race, what are the ATP sources?

- Ultrarapid immediate system



This man practices jogging every morning, what are the ATP sources?

- ***Long term aerobic system***
- **Fuel:** glucose mainly
- ***Oxygen source:***
  - Directly from blood
  - Stored in myoglobin (muscle oxygen containing molecule)

What is Oxygen debt

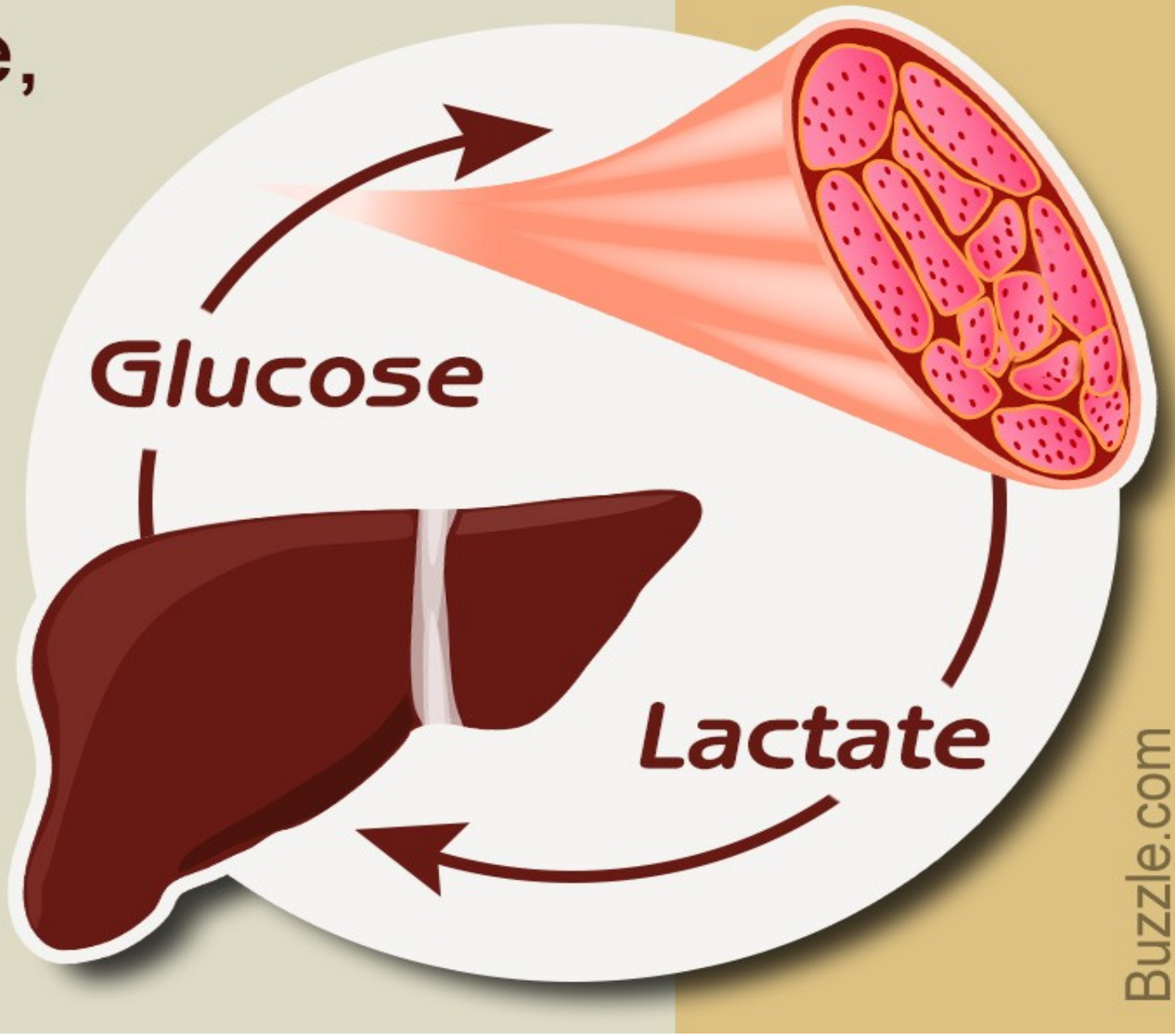
- **Definition**:
- Extra-amount of O2 that must be taken into the body during recovery period after muscular exercise
- **Recovery period:** from end of exercise till the return of heart and respiratory rate to normal.
- **Aim** To restore all the metabolic systems back to their full normal state.

Types of oxygen debt

Lactic acid O2 debt	**alactic O2 debt**
Greater amount of O2	**Smaller** amount of O2
Takes about **1 hour** or more	It is fully rapid **within 2-3 minutes**
➢ Remove excess lactic acid from the muscles and all body fluid. ➢ Convert lactic acid to pyruvic acid and glucose	➢ Replenish ATP stores ➢ Restore creatine phosphate (CP) ➢ Rebind to myoglobin

Note: Trained subjects have lower oxygen debt due to better aerobic capacity, less lactic acid production

In the cori cycle, **lactate** produced by the muscles is converted to **glucose** by the liver, and fed back to the muscles.



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Muscle fatigue

- It is the temporary decrease in muscle force of contraction due to previous contractile activity.
- **Causes of fatigue:**
- **A) Muscular fatigue:**
- Lactic acid accumulation: increase in the intracellular acidity and inhibit key enzymes in energy pathways.
- Energy stores depletion
- **B) Neuromuscular fatigue:**
- Acetyl choline depletion at the motor end plate during fast-powerful activities.
- **C) Central psychological fatigue:**
- Central nervous system no longer adequately activates the motor neurons supplying the working muscles.
- Athlete’s performance is not only dependent on the physical state of his muscles, but also, upon the **well to win** “ability to overcome psychological fatigue”.

Summary

- ATP is the main muscle energy source
- Exercise first few seconds: Ultra rapid phosphagen system.
- First few minutes or at the end of the exercise: short term anaerobic system {anaerobic glycolysis}
- Long term endurance exercise: aerobic glycolysis
- Oxygen debt: Extra-amount of O2 that must be taken into the body during recovery period
- A lactic oxygen debt rapid to replenish ATP, CP and myoglobin
- Lactic oxygen debt prolonged to remove muscle lactic acid and convert it to glucose

SUGGESTED TEXTBOOKS

1. **Guyton and Hall Textbook of Medical Physiology.**
   https://www.amazon.com/Guyton-Hall-Textbook-Medical-Physiology/dp/1455770051

2. **Ganong's Review of Medical Physiology, 25e.**

   https://www.amazon.com/Ganongs-Review-Medical-Physiology-Twenty-Fifth/dp/007182510X

3. **USLME step 1 lecture notes physiology 2017.**
   https://drive.google.com/drive/folders/1b6hSiwAzGyRypOTDCnnBw68MmQEVRv-u?usp=sharing

Well done